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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Yukio Yamori, et al.
Appl. No.	:	09/890,416
Filed	:	July 27, 2001
For	:	DRUGS, FOODS AND ORAL COMPOSITIONS CONTAINING STILBENE-TYPE COMPOUNDS
Examiner	:	Unknown

09/890 416

Group Art Unit Unknown

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on

DEA 10/9/01

October 9, 2001
(Date)

Daniel E. Altman, Reg. No. 34,115

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LETTER

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Enclosed for filing in the above-referenced application is a translation of Form PCT/IPEA/409.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 9 Oct. 2001

By: Daniel Altman

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Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P00-01	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP00/00454	International filing date (*day/month/year*) 28 January 2000 (28.01.00)	Priority date (*day/month/year*) 29 January 1999 (29.01.99)
International Patent Classification (IPC) or national classification and IPC A61K 31/05, 31075, 31/136, 31/155, 31/185, 31/192, 31/343, 31/70, 35/78, A61P 19/10, 9/12, 19/08, 9/10, A23L 1/30, 1/302, 1/303, 1/304		
Applicant SUNSTAR INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14 July 2000 (14.07.00)	05 March 2001 (05.03.2001)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

Form PCT/IPEA/409 (cover sheet) (July 1998)

[redacted]

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP00/00454

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-7,9,11-25, as originally filed
pages _____, filed with the demand
pages 8,10, filed with the letter of 21 December 2000 (21.12.2000)

☒ the claims:

pages 1-15,17-19, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages 16, filed with the letter of 21 December 2000 (21.12.2000)

☒ the drawings:

pages 1-2, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP00/00454

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 11,19

because:

☒ the said international application, or the said claims Nos. 11,19 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See supplemental sheet for continuation of Box III. 1.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 11,19

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III. 1.

Claims 11 and 19 pertain to methods for treatment of the human body by therapy or surgery as well as diagnostic methods and thus relate to subject matter which this International Preliminary Examination Authority is not required to examine under the provisions of PCT Article 34(4)(a)(i) and PCT Rule 67(iv).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP00/00454

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

See supplemental sheet for continuation of Box IV. 3.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-10,12-18

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV. 3.

The compositions described in Claims 1 to 10 relate to the use of stilbene and its derivatives represented by general formula (1), which are publicly known compounds *per se*, in the prevention and the treatment of diseases associated with osteopenia.

Moreover, the compositions described in Claims 12 to 18 relate to the use of the same stilbene and its derivatives in the prevention and the treatment of hypertension and diseases caused by high blood pressure.

The prevention and the treatment of osteopenia and the prevention and the treatment of hypertension and diseases caused by high blood pressure are not based on the same pharmacological mechanism.

Therefore, there does not appear to be a relationship having a special technical feature exceeding the prior art in common between the group of inventions set forth in Claims 1 to 10 and the group of inventions set forth in Claims 12 to 18. Such being the case, it is considered that the group of inventions set forth in Claims 1 to 10 and the group of inventions set forth in Claims 12 to 18 are two groups of inventions which are not so linked as to form a single general inventive concept (PCT Rule 13.2).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP 00/00454

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims		YES
	Claims	1-10, 12-18	NO
Inventive step (IS)	Claims		YES
	Claims	1-10, 12-18	NO
Industrial applicability (IA)	Claims	1-10, 12-18	YES
	Claims		NO

2. Citations and explanations

The following Documents 1 to 9 cited in the international search report are cited in this preliminary examination report:

Document 1: MIZUTANI, Kenichi et al., "Resveratrol stimulates the proliferation and differentiation of osteoblastic MC3T3-E1 cells", Biochemical Biophysical Research Communication, Vol. 253, No. 3, (1998), pp. 859 to 863

Document 2: INAMORI, Yoshihiko et al., "The coronary vasodilatory and hypotensive effects of 3, 3',4,5'-tetrahydroxystilbene and its derivatives", Yakugaku Zasshi, Vol. 104, No. 7, (1984), pp. 819 to 821

Document 3: BELGUENDOUZ, Leila et al., "Interaction of trans-resveratrol with plasma lipoproteins", Biochemical Pharmacology, Vol. 55, No. 6, (1998), pp. 811 to 816

Document 4: SOLEAS, G.J. et al., "Resveratrol: a molecule whose time has come? and gone?", Clin. Biochem., Vol. 30, No. 2, (1997), pp. 91 to 113

Document 5: GOLDBERG, D.M. et al., "Identification and assay of trihydroxystilbenes in wine and

their biological properties", ACS Symp. Ser., Vol. 661 (Wine), (1997), pp. 24 to 43

Document 6: KRISA, S. et al., "Production, isolation and biological activity of piceids (stilbenes) extracted from Vitis vinifera cell cultures", Bull. Soc. Pharm. Bordeaux, Vol. 136, No. 1-2-3-4, (1997), pp. 7 to 18

Document 7: JIN, Dadi et al., "Polydatin protects against endotoxin shock in rats", Zhonghua Chuangshang Zazhi, Vol. 14, No. 2, (1998), pp. e20 to e24

Document 8: GERATZ, J.D. et al., "Inhibition of the amidase and kininogenase activities of pancreatic kallikrein by aromatic diamidines and an evaluation of diamidines for their in vivouse", Arch. Int. Pharmacodyn. Ther., Vol. 194, No. 2, (1971), pp. 359 to 370

Document 9: XU, G. et al., "Inhibition of protein kinase C by stilbenoids", Yaoxue Xuebao, Vol. 29, No. 11, (1994), pp. 818 to 822

Document 1 indicates that 3,3',4,5'-tetrahydroxystilbene that is included in the compound represented by general formula (1) disclosed in Claim 1 of the present application stimulates the proliferation and differentiation of osteoblastic cells. Therefore, the compound for use in the prevention and the treatment of diseases associated with osteopenia that is the invention disclosed in Claims 1 to 10 of the present application is disclosed in Document 1 and lacks novelty. Moreover, it would be obvious to a person skilled in the art in the light of the disclosures in said Document 1.

Document 2 indicates that the resveratrol (Resveratrol;3,4',5'-trihydroxystilbene) that is included in the compound represented by general formula (1)

disclosed in Claim 12 of the present application has the effect of lowering blood pressure. Therefore, the compound for use in the prevention and the treatment of hypertension and diseases caused by high blood pressure that is the invention disclosed in Claims 12 to 18 is disclosed in Document 2 and lacks novelty. Moreover, it would be obvious to a person skilled in the art in the light of the disclosures in said Document 2.

Documents 3 to 5 indicate that the resveratrol (Resveratrol;3,4',5'-trihydroxystilbene) that is included in the compound represented by general formula (1) disclosed in Claim 12 of the present application has preventative effects against arteriosclerosis, which is a disease caused by high blood pressure, as described in this application. Therefore, the compound for use in the prevention and the treatment of hypertension and diseases caused by high blood pressure that is the invention disclosed in Claims 12 to 18 is disclosed in Documents 3 to 5 and lacks novelty. Moreover, it would be obvious to a person skilled in the art in the light of the disclosures in said Document 2.

Document 6 indicates that the stilbene derivative Piceid that is included in the compound represented by general formula (1) disclosed in Claim 12 of the present application has preventative effects against arteriosclerosis, which is a disease caused by high blood pressure, as described in this application. Therefore, the compound for use in the prevention and the treatment of hypertension and diseases caused by high blood pressure that is the invention disclosed in Claims 12 to 18 is disclosed in Document 6 and lacks novelty. Moreover, it would be obvious to a person skilled in the art in the light of the disclosures in said Document 2.

Document 7 indicates that the stilbene derivative

Polydatin that is included in the compound represented by general formula (1) disclosed in Claim 12 of the present application has a protective effect against endotoxin shock and that it can improve low blood pressure. However, the technical matter of the document is not deemed directly related to the present application. We could even say that the prevention and the treatment of hypertension in the present application and the improvement in low blood pressure could suggest that they have opposing pharmacological effects.

Document 8 indicates that compounds such as stilbamidine that are included in the compound represented by general formula (1) disclosed in Claim 12 of the present application have the same inhibitory effects as compound M & B4549 and that compound M & B4549 has brought about hypotension when administered intravenously into dogs. On consideration of this disclosure, the compound for use in the prevention and the treatment of hypertension and diseases caused by high blood pressure that is the invention disclosed in Claims 12 to 18 would be obvious to a person skilled in the art.

Document 9 discloses monomers, dimers and trimers, etc. of stilbene derived from plants that are included in the compound represented general formula (1) disclosed in Claim 1 or 12 of the present application. It would be obvious to a person skilled in the art to replace the stilbene derivatives disclosed in the above-mentioned Documents 1 to 6 and 8 and apply the invention disclosed in Document 9 as the active ingredient.

The invention disclosed in Claims 1 to 10 and 12 to 18 of the present application are industrially applicable.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO,99/56737,A1[EX]	11 November 1999 (11.11.1999)	05 May 1999 (05.05.1999)	05 May 1998 (05.05.1998)

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

It is unclear what kinds of specific compounds are included in the "polymers" of the compound represented by general formula (1) disclosed in Claims 1 and 12.

Among the compositions disclosed in Claims 1 to 8, 10 and 12 to 17, when the active ingredient is the above-mentioned "polymer", the international search report has been produced based on the compound that is specifically named on page 8, lines 17 to 22 of the description. Therefore, this written opinion has been produced based on the results of said search.

Claim 16 discloses a composition for use in the prevention and the treatment of arteriosclerosis having as the active ingredient the compound of general formula (1) containing Resveratrol. However, the document "WILSON, Ted et al., "Resveratrol promotes atherosclerosis in hypercholesterolemic rabbits", Life Sciences, Vol. 59, No. 1, (1996), PL15 to PL21" cited in the international search report indicates that the above-mentioned Resveratrol actually promotes atherosclerosis, thus suggesting an effect opposite to that of this application.